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Pillsbury Winthrop LLP
Intellectual Property Group
11682 El Camino Real, Suite 200
San Diego, CA 92130-2593

EXAMINER	
LE, EMILY M	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 05/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/910,483	FANG ET AL.	
	Examiner	Art Unit	
	Emily Le	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-83* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-83* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/10/03, 10/14/03, 11/10/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Miscellaneous

1. The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1648, Examiner Emily Le.

2. In addition, upon further consideration of the claims, the disclosure of the instant specification, and the references that was cited as enabling the instantly claimed invention, a humanized antibody that inhibits coxsackie A virus, HRV, and RSV; it is determined that the scope of enablement that was granted to Applicant by the previous Examiner of record, is hereby withdrawn. The Examiner regrets any inconvenience this may cause Applicant, however, it is determined that a full scope of enablement is necessary.

Sequence Compliance

3. The instant application continues to be in non-compliance with the sequence rules because the data presented in the sequence listing does not contain the same sequences taught in the specification. For example, from the submitted listing, SEQ ID NO: 37 contains 116 amino acids, however, the drawings--as originally filed indicates that the amino acids present contains no more than 113 amino acids. The sequence listing contains new matter because it introduces amino acid sequences that were not originally filed with the application. Furthermore, it does not appear that a "SEQ ID NO:" is assigned to the amino acids of the antibody that is denoted as IA6. Therefore, it is deemed that the communication filed 11/10/03 is not fully responsive to the previous

Office communication for the reason(s) set forth below or on the attached Notice To Comply With The Sequence Rules or CRF Diskette Problem Report. Applicant is given the same response period as the instant office action to place the instant application in sequence compliance.

Drawings

4. New corrected drawings are required in this application because "SEQ ID NO:" is not appended next to all instances of either amino acid or nucleic acid sequence listing. In addition, it is noted that the description of Figure 3 in the specification is not consistent with what is presented in Figure 3. Figure 3 presents the amino acids sequence of humanized 1A6 (HUM19), not HUMB. There is an inconsistency in the labeling. Applicant is advised to employ the services of a competent patent draftsperson outside the Office, as the U.S. Patent and Trademark Office no longer prepares new drawings. The corrected drawings are required in reply to the Office action to avoid abandonment of the application. The requirement for corrected drawings will not be held in abeyance.

Specification

5. The previous objection to the disclosure due to the brief description of Figure 2 making reference to colors is withdrawn in view of Applicant's submission of color photographs.

6. Applicant is advised to update the status of all related applications disclosed on lines 5-7 of page 1 of the specification.

7. The disclosure is objected to because of the following informalities:

Specification, page 2, line 11, the term "variant" is misspelled.

Specification, page 2, line 21, the term "particular" is misspelled.

Specification, page 2, line 24, the term "coxsackie" is misspelled.

Specification, page 3, line 11, the terms "form" and "amino" is misspelled.

Specification, page 3, line 17, the term "particular" is misspelled.

Specification, page 4, lines 4, 12 and 20, the term "intranasally" is misspelled.

Specification, page 4, line 12, the term "intranasally" is misspelled.

Specification, page 36, lines 39; page 41, above "Table 3. Amino Acid Sequences of Humanized Antibody", the recitation of "a piece of" does not adequately describe which portion of the respective amino acid sequence that the disclosed amino acids correspond. Applicant must specify the residues in which the short amino acids, ADSVK and DPKVQ, correspond.

Specification, page 13, line 30, the terms "polylysine" and "polyglutamic" are misspelled.

Specification, page 17, line 13, the term "polynucleosides" is misspelled.

Specification, page 48, lines 28-29, the text incorrectly points to Table 2 and Figure 4 for disclosure of data gathered for Example 5. It is noted that Table 4 and Figure 5 that may be related to Example 5. In addition, the antibody designation that is provided in Table 4 is not consistent with those presented throughout the specification. For the purpose of compact prosecution, the Examiner interprets Hsc as the equivalent of Hum and that any letter that follows each of those designation are equivalent of one another. For example, HscA in Table 4 is translated to HumA. Furthermore, the

specification is objected to because the designation that is presented in Table 4 and it's translated terminology, HscA in Table 4 is translated to HumA, is not present in Figure 5. Figure 5 presents the results of antibodies with a different designation than those presented throughout the specification. It is unclear from this Figure which antibody corresponds to which humanized antibody, HumA-I.

Appropriate correction is required.

Claim Objections

8. The previous objection to claims 1, 12, 16, 22 and 47 is withdrawn in view of Applicant's deletion of limitations that is not directed to the claimed invention, and deletion of ";". However, the objection concerning the spelling of "intranasally" in claim 47 stands. Currently as amended, "intranasally" is misspelled.

9. Claims 2-3 and 22 are objected to because of the following informalities: It is strongly suggested that Applicant replace the term "subsequence" for "fragment" because "fragment" is a more acceptable and recognized term in the antibody art. This also affects claims 23-33 and 40-57,

10. Claims 47, 50 and 55 are objected to because of the following informalities: the term "intranasally" (line 2) is misspelled.

11. Claim 48 is objected to because of the following informalities: the term "inhibit" is repeated twice (line 3).

12. Claims 63-72 are objected to because of the following informalities: It appears that the claims are intended to recite CDR, Howe ever, currently as written, the claims only recite "complementarity regions", not "complementarity determining regions".

13. Claims 2-3 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The claims do not further limit the antibody of the claim 1, to which the instant claims depend. Claim 1 is directed to a humanized antibody. Claim 2-3 are directed to further broaden claim 1 by reciting a fragment of claim 1, wherein claim 1 does not include fragments. Appropriate correction is required.

Claim Rejections - 35 USC § 112

14. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

15. The lack of antecedent basis for "the humanized antibody of claim 2" rejection in claim 3 is withdrawn.

16. Claims 1-83 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 and all claims that depends from the claim, is rendered indefinite because it is unclear from the current recitation, "said antibody selected from: SEQ ID NO: 5 and 7" if the claim is directed to an antibody that is i) solely defined by SEQ ID NO: 5, ii) solely defined by SEQ ID NO: 7, or iii) defined by a combination of SEQ ID NO: 5 and 7.

There is insufficient antecedent basis for the following limitations in the following claims:

- Claim 2 and all claims that depends from the claim, recites the limitation "the variable framework region" in line 2.
- Claim 4 and all claims that depend from the claim, recites the limitation "the variable framework region" in line 2.
- Claim 5 and all claims that depends from the claim, recites the limitation " the variable framework region" (line 2) and "the protective efficacy" (line 3).
- Claims 6-10 and all claims that depend from the claim, the claims recite the limitation " the non-humanized antibody " (line 2) of the claims.
- Claim 22 and all claims that depend from the claim, recites the limitation " the variable framework region" in line 6. In addition, the claims are rendered indefinite because it is unclear from the current recitation, "said the amino acid sequence set forth in any of SEQ ID NO: 5 and 7" if the claim is directed to an antibody that comprises i) SEQ ID NO: 5, ii) SEQ ID NO: 7, or iii) a both SEQ ID NO: 5 and 7.
- Claim 28 and all claims that depend from the claim, recites the limitation " the variable framework region" in line 2.
- Claim 31 and all claims that depend from the claim, recites the limitation " the vector" in line 1.

- Claim 33 and all claims that depend from the claim: the claim recites the limitation "the cell " (line 1) of the claim.

Claims 13-21, currently as written it is unclear which antibody, the humanized or mouse monoclonal antibody, is directed to by the recitation of "the antibody".

Claims 52 and 57 and all claims that depend from the respective claims, currently as written, it appears that the overall range is from 1 to 18. However, because of the different segmented groups, it is unclear what is intended or encompassed by the groups. Furthermore, because the claims contain recitation is that directed to a newborn, it is unclear the time unit that is associated with each group. In other words, it is in the form of days, weeks, months, or years?

Claim 53 and all claims that depend from the claim: it is unclear what the metes and bounds are for the recitation of "one or more symptoms". It is unclear which symptom(s) is encompassed by such recitation. Furthermore, it is unclear how a decrease of one or more symptoms of the common cold can occur if the subject does not have the cold or show signs of any cold symptoms. Moreover, it is unclear how inhibition of one or more symptoms of the cold can be achieved if the subject has the cold. In addition, it is unclear what the metes and bounds are of the term "decrease". It is unclear how a decrease in one or more cold symptom(s) can be achieved and what parameters can be used to measure a "decrease".

Claims 63-83, currently as written, it is unclear which antibody, the humanized antibody that is recited in claims 1 and 4 or the substituted antibody that is recited in claim 4, is intended by "wherein the antibody". Furthermore, if the recitation is directed

to the humanized antibody that is recited in claim 1, then it is unclear how the instant humanized antibody, which is made up of the complementarity determining regions of mouse monoclonal antibody denoted as 1A6, can have a better affinity for ICAM-1 than "humanized antibody having the complementarity [determining] regions of mouse monoclonal antibody denoted as 1A6".

Claims 72 and 83, it is unclear what is intended by the following recitation: "100 fold or greater than". Currently as written, it recites on a range that is beyond 100 fold, however, it is unclear if the affinity activity is supposed to decrease or increase by a range that is beyond 100 fold when it is compared to the other antibody.

Therefore, because of the reasons cited above, the claims are rendered indefinite.

17. Claims 5, 63, 71-73 and 82-83 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 5 and 73: Support cannot be found for the recitation of "is at least equivalent", line 4 of the claim. It is acknowledge that the specification teaches "greater or less affinity", however, such recitation do not support "is at least equivalent".

Claims 71 and 82: Support cannot be found for the recitation of "50 to 100", line 2 of the claim. It is acknowledge that the specification teaches "...20- to 100-fold

or greater than the parental antibody", however, such recitation do not support "50 to 100". Although the specification teaches a specific target range of 20-100 fold, there is no specific teaching of a species with the range. Therefore, "50 to 100" constitutes as new matter.

18. Claims 2-3 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 2-3 are directed to fragments of HumB, a humanized antibody that binds to ICAM-1 comprising a VH domain consisting of SEQ ID NO: 5 and a VL domain of consisting of SEQ ID NO: 7. The claims do not require that the fragments possess any particular distinguishing feature, biologic activity, or conserved structure. Therefore, the claims are drawn to a genus of fragments that are defined only by the identity of the fragments to the amino acid sequence of the humanized antibody, HumB.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claims is the fragments are derived from HumB. There is not even identification of any particular portion, in the

claims, of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of fragments, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of making the antibody and it's fragments. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of making the antibody and it's fragments. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only humanized antibody that binds to ICAM-1 comprising a VH domain consisting of SEQ ID NO: 5 and a VL domain of consisting of SEQ ID NO: 7 and fragments thereof that binds to ICAM-1, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

19. Claims 4 and 58-83 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to a genus of antibody that can be derived from HumB via one or more amino acid substitution. The claims also require that the binding affinity of the newly derived antibodies to ICAM-1 be more than that of the binding affinity of a mouse monoclonal antibody denoted as IA6 and any humanized antibody that comprises the CDR regions of 1A6. The claims further limits the binding affinity level to be 4-fold greater, 5-fold greater, 5 to 8-fold greater, 5 to 10-fold greater, 8 to 15-fold greater, 10 to 20-fold greater, 20 to 40-fold greater, and 100-fold or greater.

However, the specification only teaches 6 different antibodies that have a greater binding affinity than that of a humanized antibody that have the CDR regions of mouse monoclonal antibody denoted as 1A6, see Table 1.

	Binding Affinity (BA)	**(BA of HumH/BA of HumA-D, F, and I, respectively)**

HumH	2.09E-08	1.00
HumD	2.33E-08	1.11
HumB	2.62E-08	1.25
HumF	4.60E-08	2.20
HumC	5.80E-08	2.78
HumA	1.50E-07	7.18
HumI	1.50E-07	7.18

Table 1

The data that is presented in Table 1 of the instant office action is obtained from the data that is presented in Table 4 of the specification of the instant application, page 47. The difference, beside the labeling, between the data that is presented in Table 1 of the instant office action and Table 4 of the specification of the instant application is the last column, (BA of HumH/BA of HumA-D, F, and I, respectively). This data that is presented on this column indicate that Applicant taught only 6 different antibodies (HumD, B, F, C, A, and I) that have a greater affinity for ICAM-1 than that of a humanized antibody that have the CDR regions of 1A6, HumH. Furthermore, the data also indicate that the maximum level of antibody to ICAM-1 binding affinity for HumD, B, F, C, A, and I is no more than 7.18 folds greater than that of HumH, a humanized antibody that comprises the CDR regions of 1A6.

additionally, the specification does not teach any antibody, humanized or non-humanized antibody that have a greater binding affinity than that of mouse monoclonal antibody denoted as 1A6, see Table 2.

	Binding Affinity (BA)	**(BA of 1A6/BA of 1A6, HumA-D, F, and H-I, respectively)**
Mouse monoclonal antibody, 1A6	1.18E-06	1.00
HumA	1.50E-07	0.13

HumB	2.62E-08	0.02
HumC	5.80E-08	0.05
HumD	2.33E-08	0.02
HumF	4.60E-08	0.04
HumH	2.09E-08	0.02
HumI	1.50E-07	0.13

Table 2

Like Table 1 of the instant office action, the data that is presented in Table 2 of the instant office action is obtained from the data that is presented in Table 4 of the specification of the instant application, page 47. The difference, beside the labeling, between the data that is presented in Table 2 of the instant office action and Table 4 of the specification of the instant application is the last column, **(BA of 1A6/BA of 1A6, HumA-D, F, and H-I, respectively)**. This data that is presented on this column indicate that Applicant has not taught any antibody (HumD, B, F, C, A, and I) that have a greater affinity for ICAM-1 than that of 1A6, which contradicts Applicant's assertion that the binding "studies revealed that all of the humanized [singe chain antibody protein] demonstrate greater than ten times higher binding affinity for ICAM-1 than the parental mouse [1A6]".

The number of antibodies that are taught in the specification does not adequately nor does it sufficiently represent the genus of antibody that can be are derived from HumB. Furthermore, Applicant has not provided the specific activities that the newly derived antibody must possess to allow one skilled in the art to recognize the antibody that are referred to in this instantly claimed invention. It is acknowledged that the claims require that the newly derived antibody be capable of binding to ICAM-1. However, currently as written, the claims do not require that newly derived antibody to

possess a particular activity because the term capable is a conditional term. Newly derived antibodies that are capable of binding to ICAM-1 do not necessarily mean that the newly derived antibodies bind to ICAM-1.

20. Claims 4 and 58-62 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for any antibody that can be derived from HumB, via one or more amino acid substitution, wherein the newly derived antibody binds to ICAM-1 and that the CDR regions of the humanized antibody is conserved in the newly derived antibody. The specification does not reasonably provide enablement for any antibody that is derived from HumB via one or more amino acid substitution that does not bind to ICAM-1 and wherein the CDR regions of the humanized antibody is not conserved in the newly derived antibody.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. In Genentech *Inc. v. Novo Nordisk* 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997); *In re Wright* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); See also *Amgen Inc. v. Chugai Pharm. Co.,* 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir. 1991); *In re Fisher* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Further, in *In re Wands* 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) the court stated:

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman* [230 USPQ 546, 547 (Bd Pat App Int 1986)]. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The nature of the invention is directed to any antibodies that can be derived, via one or more amino acid substitution, from HumB.

The claims do not require that the newly derived antibody possess any particular distinguishing feature, biologic activity, or conserved structure. While is acknowledged that the claims contain the limitation, "capable of binding to ICAM"; however, the recited limitation does not necessarily require the newly derived antibody to possess an activity, such as binding to ICAM-1. This is so because any antibody that is capable of binding to ICAM-1 does not necessarily bind to ICAM-1. Therefore, the claims are drawn to a genus of antibody that are defined only by the condition that the newly derived antibody be derived HumB via one or more amino acid substitution. Hence, the breadth of the claims is directed to any antibody that is derived from HumB via one or more amino acid substitution; wherein the amino acid substitution can occur within or outside of one or all of the CDR regions.

The specification does not contain any working examples of antibodies, humanized or non-humanized antibody that is derived from the above humanized antibody, wherein the amino acid substitution occurs inside the CDR regions of the above humanized antibody. The specification only teaches various humanized antibodies that binds to ICAM-1, however, these humanized antibody comprises the same CDR regions, which controls the binding specificity of the antibody. There is no working example that is directed to any antibody that comprises CDR regions that are less than 100% identical to those taught in the specification.

One skilled in the art would know how to make substitution to the antibody within or beyond the CDR regions; however, one skilled in the art would not know how to use the claimed antibody because the claims encompass an unreasonable number of inoperative polypeptides, antibodies that can be derived from HumB via one or more amino acid substitution within and/or outside the CDR regions. Furthermore, the skilled artisan would not know how to use the genus of antibody that is instantly claimed because the claims do not require that the regions that controls the binding specificity of the humanized antibody to be retained.

It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of

the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al.[1] Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function.

The skilled artisan would not know how to make non-identical antibodies on the basis of teachings in the prior art or specification unless they possessed the noted activities taught in the disclosure-binds to ICAM-1. The claims are unduly broad because they do not require the newly derived antibody to retain the CDR regions of the humanized antibody to which it is derived from and because the claims have no functional limitation. For these reasons, which include the complexity and unpredictability of the nature of the invention and art in terms of the diversity of antibodies that can be derived from HumB via one or more amino acid substitution; and lack of knowledge about function(s) of encompassed fragments derived from the above

[1] Rudikoff et al. Single amino acid substitution altering antigen-binding specificity. Proc Natl Acad Sci

humanized antibody, the limited working examples of the above humanized antibody and it's one activity, the lack of direction or guidance for using any antibody that does not have the same CDR regions as those presented in the specification, and the breadth of the claims for structure without function, it would require undue experimentation to use the claimed invention that commensurate in scope with the claims.

A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F. 2d 1557, 1562, 27 USPQ 2d 1510, 1513 (Fed. Cir. 1993).

21. Claims 2-3 are also rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for HumB and fragments thereof that binds to ICAM-1. The specification does not reasonably provide enablement for fragments of HumB that do not bind to ICAM-1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with the claimed invention for the same reasons that is set forth above for the scope of enablement for claims 4 and 58-62.

22. Claims 5-15, 16(in part), 17-21(in part), 22-27, 28-33(in part), 34-39 (in part), and 40-57 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described

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SA, 1982, Vol 79, page 1979-1983, see abstract.

in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to a humanized antibody that binds to ICAM-1 and inhibits pathogen infection of cells expressing ICAM-1, including HumB; pharmaceutical composition and method of use for the humanized antibody in a subject. The claims also recite HRV, RSV, and coxsackie A virus as the pathogens. The claims additionally include inhibiting HRV progression and treating HRV infection, and decreasing or inhibiting one or more symptoms of the cold. The claims defines the subject as one that has or is at risk of having asthma, newborn, subjects that is between the ages of 1-18, or one that have or at risk of having HRV infection. The claims further requires that the humanized antibody have various level of protective efficacy greater than mouse monoclonal antibody denoted as 1A6. The claims later include nucleic acid that encodes the humanized antibody that binds to ICAM-1 and inhibits pathogen infection of cells expressing ICAM-1.

The nature of the invention is directed at therapeutic humanized antibody that binds to ICAM-1 and inhibits pathogen infection of cells expressing ICAM-1.

A pathogen is defined as an agent, such as a microorganism that can produce a disease through an infection of the host; this encompasses bacteria, fungi, and viruses as a pathogen. Therefore, in view of the definition of "pathogen", the breadth of the claims encompasses any humanized antibody that binds to ICAM-1 and inhibits any pathogen--including bacterial, fungal, parasitic, and viral infection of any cells that

expresses ICAM-1 in all subjects. The breadth of the claims encompass in vitro, in vivo, and ex vivo use of the claimed antibody.

The specification teaches how to make humanized antibodies that binds to ICAM-1. The specification also teaches humanized antibodies that have binding affinity to ICAM-1. Therefore, the enablement rejection and analysis is not focused on the how to make, humanized antibodies that have binding affinity to ICAM-1, aspect of the claimed invention. The enablement analysis is focused on the how to use aspect of the claimed invention.

The specification does not teach any humanized antibody that binds to ICAM-1 and inhibits pathogen infection of cells expressing ICAM-1. The specification does not teach the in vivo or ex vivo administration of the claimed antibody to any subjects, including subjects that has or is at risk of having asthma, newborn, subjects that is between the ages of 1-18, and subjects that have or at risk of having HRV infection.

The specification contains one example that is directed to measuring the protective efficacy of humanized antibody that binds to ICAM-1 against human rhinovirus (HRV). However, the teaching that can be derived, if any, from this example does not commensurate with the scope of the claims for several reasons. The first and primary reason is that it is unclear what activity the example measures. The example indicates an absorbance level was measured and the equation that is used to calculate the percentage of protection achieved. However, it is unclear how and what kind of absorbance activity was measured and how it correlates with percentage of protection calculated. Furthermore, it is unclear how the calculated percentage of protection fare

for different types of viruses and cells lines that expresses different levels of ICAM-1, if any, and how it correlates to an in vivo and ex vivo use of the claimed invention.

In addition, the cells that are used in the instant example are HeLa cells. HeLa cells are cancer cells that are derived from the cervix. It is unclear if the cells that is used in the instant example is appropriate for the pathogen that it is used in this example. Furthermore, it is unclear from the art if HRV infects HeLa cells. Moreover, it is unclear if HeLa cells express ICAM-1. Additionally, it is unclear from the art if ICAM is a coreceptor for all pathogens that is encompassed by the claimed invention, beside a HRV[2] and a subgroup of rhinoviruses.[3]

Additionally, the specification does not teach that the administration, in vivo, in vitro, or ex vivo, of the claimed humanized antibody to any subjects, beside the administration of HRV to HeLa cells--which is discussed above, to inhibit HRV progression, treat HRV infection, decreases or inhibits one or more symptoms of the cold, inhibit HRV infection, inhibit RSV infection, inhibit coxsackie A virus infection, or the inhibition of any other infections that are caused by any pathogens.

Moreover, because of the broadness of the pathogen that is encompassed by the claims. The claims read on a humanized antibody that binds to ICAM-1 which also inhibits HIV-1 infection. This is so because it has been demonstrated that ICAM-1 is

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[2] Ockenhouse et al. Plasmodium falciparum-infected erythrocytes bind ICAM-1 at a site distinct from LFA-1, MAC-1, and Human Rhinovirus. Cell 68 (1), 1992, pp. 63-69.

[3] Cruse et al. Illustrated dictionary of immunology, 2nd edition. CRC Press, 2003, pp. 341.

expressed on the envelope of HIV-1[4]. Therefore, the claims read on a humanized antibody that inhibits HIV infection.

It is well known in the art that retroviral infections in general, and HIV infections in particular, are refractory to anti-viral therapies. The obstacles to therapy of HIV are well documented in the literature. These obstacles include: 1) the extensive genomic diversity and mutation rate associated with the HIV retrovirus, particularly with respect to the gene encoding the envelope protein; 2) the fact that the modes of viral transmission include both virus-infected mononuclear cells, which pass the infecting virus to other cells in a covert manner, as well as via free virus transmission; 3) the existence of a latent form of the virus; 4) the ability of the virus to evade immune responses in the central nervous system due to the blood-brain barrier; and 5) the complexity and variation of the pathology of HIV infection in different individuals. The existence of these obstacles establish that the contemporary knowledge in the art would not allow one skilled in the art to use the claimed invention with a reasonable expectation of success and without undue experimentation.

Further, it is well known in the art that individuals infected with HIV produce neutralizing antibodies to the virus, yet these antibodies are not protective and do not prevent the infection from progressing to its lethal conclusion. Further, as taught by Fahey et al., clinical trials using a variety of immunologically based therapies have not yielded successful results in the treatment and/or prevention of HIV infection.[5] Fahey et

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[4] Bastiani et al. Host cell-dependent alterations in envelope components of human immunodeficiency virus type 1 virions. Journal of Virology, May 1997, pp. 3444-3450.

[5] Fahey et al. A Status of immune-based therapies in HIV infection and AIDS, Clinical and Experimental Immunology, Vol. 88 (1992), pages 1-5.

al. particularly discloses that monoclonal antibody therapies have not provided any clinical benefits and "it is not clear how adding these additional antibodies would make a difference" (see page 3, second column, third full paragraph). The failure of all immune-system-boosting therapies for treating AIDS is further discussed by Fox.[6] Thus, it is clear from the evidence of Fahey et al. and Fox, that the ability to treat and/or prevent HIV infection is highly unpredictable and has met with very little success.

In addition, there is currently no vaccine for RSV. Crowe et al. [7]review the state of the art for respiratory syncytial virus vaccine development and discuss the obstacles for developing an effective vaccine, see Table 1 on page S33. These include the lack of a sufficient animal model that is fully susceptible to infection, the young age of humans at which severe disease takes place and the safety concerns regarding immunization due to the under-developed immune responses. Other obstacles include the presence of maternal antibodies inhibiting vaccination in infants and mucosal immunity to respiratory viruses being short-lived and incomplete. Crowe et al. also teach that serum antibodies that protect the lower respiratory tract against RSV infection have little effect on upper respiratory tract infection.

Therefore, in view of the discussion above, Applicants have not provided any convincing evidence that their humanized antibody is indeed useful inhibition of any pathogen, including HIV, in vivo, in vitro, or ex vivo and have not provided sufficient guidance to allow one skilled in the art to practice the claimed invention with a

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[6] Fox, J. No Winner against AIDS. Bio/Technology, Vol. 12 (Feb 1994), page 128.
[7] Crowe et al. Vaccine. 2002; 20: S32-S37.

reasonable expectation of success and without undue experimentation. In the absence of such guidance and evidence, the specification fails to provide an enabling disclosure.

Claim Rejections - 35 USC § 103

23. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

24. Claims 1-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Colonno et al. and Padlan.

The claims are directed to a humanized antibody that binds ICAM-1 comprising a VH domain consisting of SEQ ID NO: 5 and a VL domain of consisting of SEQ ID NO: 7; and fragments thereof, including Fab, Fab' or $(Fab)_2$; wherein the variable framework region of the fragments of the humanized antibody has one or more amino acids of a human consensus variable framework region sequence.

Colonno et al. teaches the sequence of mouse monoclonal antibody 1A6. The mouse monoclonal antibody 1A6 of Colonno et al. was demonstrated to have a binding affinity to ICAM-1. The humanized antibody of the instantly claimed invention is synthesized based on the CDR regions of the mouse monoclonal antibody 1A6 of Colonno et al., lines 9-14, page 34 of specification.

Colonno et al. does not teach a humanized version of mouse monoclonal antibody 1A6 of Colonno et al.

However, Padlan teaches human consensus sequences. The humanized antibody of the instantly claimed invention is synthesized based on the human consensus sequences, lines 27-30 of page 6, lines 1-8 of page 7, and lines 17-21 of page 34 of the specification.

Therefore, at the time the claimed invention was made, it would have been obvious for one of ordinary skill in the art to combine the teachings of Colonno et al. and Padlan to produce a humanized version of mouse monoclonal antibody 1A6 of Colonno et al. and fragments thereof, including Fab, Fab' or $(Fab)_2$.

One of ordinary skill in the art would have been motivated to humanize the antibody of Colonno et al. so that the antibody of Colonno et al. can be used for therapeutic purposes in human.

One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for combining the teaching of Colonno et al. with Padlan because Colonno et al. teaches the CDR regions, the regions that is responsible for binding specificity--ICAM-1, of the mouse monoclonal antibody 1A6 that the instant humanized antibody is based; and Padlan teaches the human consensus sequence that the framework of the instant humanized antibody is based upon, to produce a humanized version of mouse monoclonal antibody 1A6 of Colonno et al. with the same binding specificity. Therefore, one of ordinary of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of producing the claimed invention absent unexpected results to the contrary.

25. Claims 4 and 53-83 are rejected under 35 U.S.C. 103(a) as being unpatentable over Colonno et al. and Padlan.

The relevance of Colonno et al. and Padlan is discussed above.

The claims are directed to any humanized antibody that is derived, via one or more amino acid substitution, from a humanized antibody that binds ICAM comprising a VH domain consisting of SEQ ID NO: 5 and a VL domain of consisting of SEQ ID NO: 7; wherein the derived humanized antibody is capable of binding to an ICAM-1 epitope. The claims also require that the substitution occur in the CDR region of the initial humanized antibody, in the framework region. The claims also limit the number of amino acid substitution to 5-10, 3-5, and 1-3 amino acids. The claims also requires that the derived humanized antibody to have an increased affinity, binding affinity 4-fold greater, 5-fold greater, 5 to 8 fold greater, 5 to 10 fold greater, 8 to 15 fold greater, 10 to 20 fold greater, 20 to 40 fold greater, and 100-fold or greater than the binding affinity of i) a mouse monoclonal antibody that is denoted as 1A6 to ICAM-1 and ii) a humanized antibody having the CDR regions of a mouse monoclonal antibody that is denoted as 1A6 to ICAM-1.

At the time of the claimed invention, it would have been obvious to one of ordinary skill in the art to take the humanized antibody that is produced by combining the teachings of Colonno et al. and Padlan and make different amino acid substitutions within the humanized antibody produced by the combining the teachings of Colonno et al. and Padlan as part of routine experimentation.

One of ordinary skill in the art would have been motivated to do so to determine the effect of the substitution on the activity of the humanized antibody, such as immunogenicity and affinity of the antibody to ICAM-1.

One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for doing so because such manipulation is part of routine experimentation. Therefore, one of ordinary of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of producing the claimed invention, absent unexpected results to the contrary.

26. Claims 16-21 (in part) are rejected under 35 U.S.C. 103(a) as being unpatentable over Colonno et al. and Padlan.

The relevance of Colonno et al. and Padlan is discussed above.

The claims are directed to a humanized antibody that binds ICAM-1 comprising a VH domain consisting of SEQ ID NO: 5 and a VL domain of consisting of SEQ ID NO: 7; The claims also require that the humanized antibody be multispecific or multifunctional, the humanized antibody to be linked to one or more identical or different antibodies to form a multimer--wherein the multimer comprises a homo- or hetero-dimer, trimer, or tetramer; wherein the multimer is formed via a multimerization domain, wherein the multimerization domain comprises a human amino acid sequence. The humanized antibody be further comprises a linker that is located between the multimerization domain and the antibody.

At the time of the claimed invention, it would have been obvious to one of ordinary skill in the art to take the humanized antibody that is produced by combining

the teachings of Colonno et al. and Padlan and make produce a multispecific or multifunctional humanized antibody, link the humanized antibody to one or more identical or different antibodies to form a multimer--wherein the multimer comprises a homo- or hetero-dimer, trimer, or tetramer; wherein the multimer is formed via a multimerization domain, wherein the multimerization domain comprises a human amino acid sequence; and wherein the linker that is located between the multimerization domain and the antibody.

One of ordinary skill in the art would have been motivated to do to produce a humanized antibody that have multiple binding specificity to different antigens.

One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for doing so because such manipulation is part of routine experimentation. Therefore, one of ordinary of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of producing the claimed invention, absent unexpected results to the contrary.

27. Claims 28-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Colonno et al. and Padlan.

The relevance of Colonno et al. and Padlan is discussed above.

The claims are directed to nucleic acid sequence that encodes the humanized antibody that binds ICAM-1 comprising a VH domain consisting of SEQ ID NO: 5 and a VL domain of consisting of SEQ ID NO: 7; expression cassette that comprises the nucleic acid sequence that encodes the above humanized antibody that is linked to an expression control element; a vector comprising nucleic acid sequence that encodes the

above humanized antibody; an d a cell comprising nucleic acid sequence that encodes the above humanized antibody, wherein the cell is further limited to prokaryotic or eukaryotic.

At the time of the claimed invention, it would have been obvious to one of ordinary skill in the art to take the humanized antibody that is produced by combining the teachings of Colonno et al. and Padlan and determine the nucleic acid sequence that encodes the humanized antibody that binds ICAM-1 comprising a VH domain consisting of SEQ ID NO: 5 and a VL domain of consisting of SEQ ID NO: 7, place it in an expression cassette, a vector; and a cell, prokaryotic or eukaryotic.

One of ordinary skill in the art would have been motivated to do all of the above to reproduce the humanized antibody obtained by combining the teachings of Colonno et al. and Padlan.

One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for doing so because such procedure is part of routine experimentation to reproduce an antibody. Therefore, one of ordinary of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of producing the claimed invention, absent unexpected results to the contrary.

28. Claims 34-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Colonno et al. and Padlan.

The relevance of Colonno et al. and Padlan is discussed above.

The claims are directed to a pharmaceutical composition comprising the humanized antibody that binds ICAM-1 comprising a VH domain consisting of SEQ ID NO: 5 and a VL domain of consisting of SEQ ID NO: 7; and a pharmaceutically acceptable carrier, wherein the carrier is compatible with inhalation or nasal delivery to a subject.

At the time of the claimed invention, it would have been obvious to one of ordinary skill in the art to take the humanized antibody that is produced by combining the teachings of Colonno et al. and Padlan and produce a pharmaceutical composition comprising the humanized antibody and a pharmaceutically acceptable carrier, wherein the carrier is compatible with inhalation or nasal delivery to a subject.

One of ordinary skill in the art would have been motivated to do so to make the humanized antibody be suitable for therapeutic uses.

One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for doing so because such procedure is part of routine experimentation. Therefore, one of ordinary of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of producing the claimed invention, absent unexpected results to the contrary.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Emily Le whose telephone number is (571) 272 0903. The examiner can normally be reached on Monday - Friday, 8 am - 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (571) 272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

E.Le

Shanon Foley
Patent Examiner, AU 1648

Notice to Comply	Application No. 09/910,483	Applicant(s) Fang et al.	
	Examiner Emily Le	Art Unit 1648	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒ 7. Other: The content of the submitted sequence listing, both paper and CRF, are not the same as those presented in the specification at the time of filing. See the attached office action for specific details.

Applicant Must Provide:

☐ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

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